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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: December 16, 2003

MEMORANDUM

TXR# 0050721

SUBJECT: **PERMETHRIN**: Toxicology Disciplinary Chapter for the Reregistration Eligibility Decision

FROM: Yung G. Yang, Ph.D.
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THROUGH: *Alberto Protzel, Ph.D.*
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TO: Carol Christensen, Risk Assessor
Reregistration Branch II
Health Effects Division (7509C

DP Barcode:	D296632	**Chemical:**	Permethrin
PC Code:	109701	**CAS No.:**	52645-53-1

ACTION REQUESTED: HED has been requested to review the toxicity database for permethrin to determine whether it is adequate to support the re-registration of permethrin.

RESPONSE: Based on the currently available toxicology data on permethrin, the Toxicology Branch concluded that the toxicity database is adequate to support the re-registration of this chemical. A toxicology chapter on permethrin has been prepared and is attached.

RC
03/04

PERMETHRIN

PC Code: 109701

Toxicology Disciplinary Chapter for the Reregistration Eligibility Decision Document

Date completed: December 16, 2003

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1.0 HAZARD CHARACTERIZATION

Permethrin (3-phenoxybenzyl-methyl-3-(2,2-dichloroethenyl)-2,2 dimethyl-cyclopropanecarboxylate) is a synthetic pyrethroid insecticide registered for use on many food/feed crops and for applications to livestock and their housing. Permethrin is a racemic mixture of the cis and trans isomers. It has been shown that increased content of cis isomer would increase its severity of clinical signs and toxicity. The current registered technical active product has a content of cis isomer ranging from 35% to 55%. The toxicology database of permethrin showed that studies of the test material have a content of cis isomer ranging from 25% to 50%. The HIARC determined that the toxicology database, with the exception of the developmental neurotoxicity study, is adequate to support the re-registration of permethrin.

Permethrin has a low acute toxicity (toxicity category 3 or 4) via the oral, dermal, or inhalation route of exposure. Permethrin is not an eye or skin irritant and not a skin sensitizer. Permethrin is a type I pyrethroid with the primary target organ being the nervous system. The neurotoxic effects are consistently characterized by tremors, hyperactivity, and altered FOB observations. In studies where the liver is affected, it appears to be an adaptive response and is not considered an adverse effect. Following oral administration, permethrin is rapidly absorbed, metabolized, and excreted in urine and feces.

Developmental and reproductive toxicity studies demonstrated that there is no evidence (qualitative or quantitative) for increased susceptibility following *in utero* and/or pre-/post-natal exposure in the developmental toxicity studies in rats and rabbits and multi-generation reproduction studies in rats. There is no evidence that permethrin induces any endocrine disruption. However, the HIARC determined that there is a concern for developmental neurotoxicity based on evidence of neurotoxicity and increased incidence of microscopic lesions associated with neurotoxic effects at high doses in a subchronic neurotoxicity study. A developmental neurotoxicity study (DNT) is required for permethrin.

In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July 1999), the CARC classified permethrin as **"Likely to be Carcinogenic to Humans"** by the oral route, with a Q_1^*(mg/kg/day)$^{-1}$ for Permethrin of 9.567×10^{-3}. This classification was based on evidence of two reproducible benign tumor types (lung and liver) in the mouse, equivocal evidence of carcinogenicity in Long-Evans rats, and supportive SAR information.

2.0 REQUIREMENTS

The requirements (CFR 158.340) for food use of permethrin are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table 1. Data requirements (CFR 158.340) for food use of permethrin

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes[1]
870.3150	Oral Subchronic (nonrodent)	yes	yes[1]
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	NA
870.3465	90-Day Inhalation	no	NA
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotox. (hen)	no	yes
870.6100b	90-Day Neurotoxicity (hen)	no	NA
870.6200a	Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b	90 Day Neuro. Screening Battery (rat)	yes	yes
870.6300	Develop. Neuro	yes	no[2]
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	yes	yes
Special Studies for Ocular Effects			
	Acute Oral (rat)	no	no
	Subchronic Oral (rat)	no	no
	Six-month Oral (dog)	no	no

1. Requirements are satisfied by chronic oral toxicity studies.
2. The HIARC determined that a developmental neurotoxicity study is required (Data gap).

3.0 DATA GAP(S)

Developmental neurotoxicity study in rats (OPPTS 870.6300)

4.0 HAZARD ASSESSMENT

4.1 Acute Toxicity

Adequacy of data base for acute toxicity: The database for acute toxicity is considered complete. No additional studies are required at this time. Permethrin has a low acute toxicity (toxicity category 3 or 4) via the oral, dermal, or inhalation route of exposure. Permethrin is not an eye or skin irritant and not a skin sensitizer. The acute toxicity data on permethrin is summarized below in Table 2.

Table 2. Acute Toxicity Data on Permethrin*

OPPTS Guideline	Study Type	MRID No.	Results	Toxicity Category
870.1100	Acute oral toxicity in Rats	242899	LD_{50} = 3580 mg/kg (M) 2280 mg/kg (F)	III
870.1200	Acute dermal toxicity in Rabbits in Rats	 242899 099258	LD_{50} >2000 mg/kg	III
870.1300	Acute inhalation toxicity in Rats	096692	LC_{50} >23.5 mg/L	IV
870.2400	Acute eye irritation in Rabbits	242899 099258	No corneal opacity or conjunctival irritation	IV
870.2500	Acute dermal irritation in Rabbits	242899 096692	All irritation cleared by 48 hrs	IV
870.2600	Skin sensitization in Guinea Pigs	099258 099263	Non-sensitizer	N/A**

* Data extracted from HED Doc. No. 008216.
** N/A: Not Applicable.

4.2 Subchronic Toxicity

Adequacy of data base for subchronic toxicity: The data base for subchronic toxicity is incomplete; however, chronic studies are available and considered adequate for risk assessment purpose. No additional studies are required at this time.

870.3100 90-Day Oral Toxicity - Rat

No acceptable study is available.

870.3100 90-Day Oral Toxicity - Mouse

No study is available.

870.3150 90-Day Oral Toxicity - Dog

No acceptable study is available.

870.3200 21/28-Day Dermal Toxicity – Rat

In a 21-day repeated dose dermal toxicity study (MRIDs 41143801, 42653301), groups of Wistar Alpk:Apfsd SPF rats (5/sex/group) were treated with undiluted Permethrin (95.6%, Batch No. Y00040/85, RS/38F). Animals were treated by dermal occlusion for 6 hours/day for 21 days at doses of 0, 50, 150, or 500 mg/kg/day.

There were no treatment-related deaths and no effects on body weight, food consumption, hematology, clinical chemistry, or gross or microscopic lesions. Increases in absolute ($p<0.05$; 10.3% increase) and relative ($p<0.05$; 10.6% increase) liver weight were noted in high-dose females only. No histopathological evidence of adaptive liver change was seen in any treatment group. Therefore, the increase of liver weight in females was not considered biologically significant. Skin irritation was observed at the application site of all treatment groups.

The systemic NOAEL was 500 mg/kg/day (the highest dose tested), the systemic LOAEL was not established. The dermal LOAEL was 50 mg/kg/day based on skin irritation. A dermal NOAEL was not identified.

This study is classified as **Acceptable/Guideline** and does satisfy the guideline requirements for a repeated-dose dermal study [OPPTS 870.3200 (§82-2)] in rats.

870.3465 90-Day Inhalation – Rat

No 90-day inhalation study is available; however, a 15-day inhalation study in rats is available. An executive summary is as follows.

In a 15-day inhalation toxicity study (MRID00096713) Permethrin (94.7% a.i., Lot # ZJ) was administered to groups of 5 male and 5 female Charles River rats/concentration by dynamic whole-body inhalation exposure at concentrations of 0, 6.1, 42.2, or 583 mg/m^3 (0.0061, 0.042, or 0.583 mg/L) for 15 exposures (6 hours/day for 2 days during week 1, 5 days during weeks 2 and 3, and 3 days during week 4).

There was no test material-related effect on mortality, body weight or weight gain, food consumption, hematology, organ weights, or gross pathology. Weight gain was actually greater in all treated groups than in the respective control groups. Clinical signs were observed in the treated groups. Two female rats in the 0.0061 mg/l group were observed to have slightly labored

breathing 30 minutes into the first exposure but not subsequently. In the 0.042 mg/l (MCT) group, licking of the inside of the mouths became more extensive then in the low-treatment group and involved most of the rats. All 5 females were observed to have slightly labored breathing during the first exposure but not subsequently. Labored breathing was not observed in male rats in either the 0.0061 or 0.042 mg/L groups. All rats in the 0.042 mg/L group appeared more alert than in the control and low-dose groups and adopted a hunched posture with open eyes during the early part of some exposures. The 0.583 mg/L group (HCT) demonstrated less activity, greater response to auditory or touch stimuli, and more extensive licking behavior than the other groups. Body tremors were observed in this group beginning with 3 females during the last hour of the first exposure and in 3 males during the second exposure. In both instances, tremors continued post exposure. The tremors reached a peak incidence, 5 males and 4 females, during the 5th exposure (3rd day of the second week) and declined thereafter, with only 1 male and 1 female showing tremors on exposure day 15 (2nd exposure of week 4). Slightly labored breathing was recorded in 1 male and 1 female in this group.

The hypersensitivity to noise or touch became evident in the 0.583 mg/L (HCT) group following the second exposure and involved 5 males and 5 females. This sign tapered off with continued exposures, but was still displayed by 3 females following the 7th exposure. Rales, poor grooming, and crusty brown staining around the nose were observed occasionally in the 0.583 mg/L group, with incidences higher in females than in males. Microscopic pathology on the lungs showed focal to diffuse pneumonitis and perivascular inflammation - although to some degree more severe in the treated groups, could not be clearly distinguished from the respiratory infection present in all animals.

On April 18, 2002, the HIARC determined that the dose/endpoint of this study can be used for risk assessment purpose because the clinical signs of neurotoxicity were observed in the first day of exposure. **The LOAEL is 0.583 mg/L in male and female rats based on body tremors and hypersensitivity to noise. The NOAEL is 0.042 mg/L.** This 15-day inhalation toxicity study in the rat is classified **acceptable/non-guideline.** This study does not satisfy the guideline requirement for a subchronic inhalation study OPPTS 870.3465

4.3 Prenatal Developmental Toxicity

Adequacy of data base for Prenatal Developmental Toxicity: The database for prenatal developmental toxicity is considered adequate. No additional studies are required at this time. There is no quantitative or qualitative evidence of increased susceptibility of rat or rabbit fetuses to *in utero* exposure in available developmental toxicity studies.

870.3700a Prenatal Developmental Toxicity Study - Rat

In a developmental toxicity study (MRID 40943603), 24 presumed pregnant Wistar rats per group were administered 0, 15, 50, or 150 mg/kg/day of permethrin (93.9% a.i.; 38 cis:62 trans isomers; Reference No. RS 78/E) by gavage on gestation days (GD) 7-16, inclusive. The vehicle

was corn oil. On GD 22, all surviving dams were sacrificed and all fetuses were weighed, sexed, and examined for external malformations/variations. All fetuses were examined for visceral anomalies and the heads cut along the fronto-parietal suture line. All carcasses were processed for skeletal examination.

All animals survived to scheduled termination and no treatment-related abnormalities were noted at gross necropsy. No maternal effects on clinical signs of toxicity, body weight gains, or food consumption were observed in the low- or mid-dose groups. In the high-dose group, clinical signs of toxicity seen between GD 8-19 included tremors in 21/24 rats and head flicking in 6/24 rats. Body weight gains by the high-dose dams were significantly ($p \leq 0.05$ or 0.01) less than that of the controls throughout the dosing interval. For GD 7-10, 10-13, and 13-16, body weight gains were decreased by 88%, 32%, and 18%, respectively, as compared with the controls. Food consumption by the high-dose group was significantly ($p \leq 0.05$ or 0.01) less than that of the controls during the dosing interval.

Therefore, the maternal toxicity LOAEL is 150 mg/kg/day based on clinical signs of toxicity and decreased body weight gain and food consumption. The maternal toxicity NOAEL is 50 mg/kg/day.

No dose- or treatment-related effects were observed on gravid uterine weights, fetal sex ratios, pre- or post-implantation losses, or numbers of corpora lutea/dam or live fetuses/dam. Mean fetal body weight of the high-dose group was 3.2% ($p \leq 0.05$) less than that of the controls. However, mean litter weight of the high-dose group was 3% (n.s.) greater than that of the controls. Therefore, the reduced fetal body weights were considered a questionable toxic response.

No treatment-related external or visceral fetal malformations/variations were noted. The fetal and litter incidence rates of short length extra ribs were significantly ($p \leq 0.05$ or 0.01) increased in the high-dose group as compared with the controls. Short length extra ribs were observed in 31% of the high-dose fetuses vs. 11% of the control fetuses and in 87% of high-dose litters vs. 57% of control litters.

Therefore, the developmental toxicity LOAEL is 150 mg/kg/day based on decrease in fetal body weights and an increase in the incidence rate of short length extra ribs. The developmental toxicity NOAEL is 50 mg/kg/day.

This study is classified as **Acceptable/Guideline** and does satisfy the requirements for a developmental toxicity study [OPPTS 870.3700 (83-3a)] in rats.

870.3700b Prenatal Developmental Toxicity Study - Rabbit

In a developmental toxicity study (MRID 92142091), presumed pregnant Dutch rabbits were administered 0, 600, 1200, or 1800 mg/kg/day of permethrin (92.5% a.i.; 32.3 cis:60.2 trans

isomers; Batch No. D108136E) by gavage on gestation days (GD) 6-18, inclusive. The number of does mated for each group was 19, 21, 20, and 23, respectively. The vehicle was 0.5% aqueous Tween 80. On GD 29, all surviving does were sacrificed and all fetuses were weighed and examined for external malformations/variations. Approximately one-half of the fetuses was processed for skeletal examination and the remaining one-half was fixed and examined for visceral anomalies. Maternal food consumption was not measured.

A total of 0, 5, 5, or 4 does died or were sacrificed moribund in the control, low-, mid-, or high-dose groups, respectively. Due to the lack of a dose-response, the deaths could not be definitively attributed to test article administration. Clinical signs of toxicity included body tremors observed in 5 of the high-dose animals only. Little or no feces or urine was noted on at least one occasion for 2/19 (11%), 4/21 (19%), 6/20 (30%), and 8/23 (35%) animals in the control, low-, mid-, and high-dose groups, respectively.

Absolute body weights were similar between the treated and control groups throughout the study. However, after examining the replotted body weight data, there was a sharp drop in weight for the low, mid, and high dose groups after day 6 and only a slight drop for the control that was noticeable after day 12. Body weight gain by the low-, mid-, and high-dose groups was 21%, 50%, and 9%, respectively, of the control level during GD 0-18 with statistical significance ($p \leq 0.05$) attained for the low- and high-dose groups. During the post-dosing interval, recovery of body weights was noted for the low- and mid-dose groups, but not for the high-dose group.

The maternal toxicity LOAEL is estimated to be <600 mg/kg/day based on decreased body weight gain. The maternal toxicity NOAEL is not identified.

The number of live fetuses and mean litter size was decreased for all dose groups compared to the control group (110(15), 80(13), 69(14), and 72(13) for control, low-, mid-, and high-dose groups, respectively). However, no dose-response was evident or statistical significance noted.

Post-implantation loss was significantly ($p \leq 0.05$) increased in the mid- and high-dose groups to 155% and 248% of the control level. Correspondingly, the number of early and late resorptions were higher in these groups as compared to the control group values (statistical significance was not reported). Mean fetal body weights in the high-dose group were slightly (-9%; n.s.) less than that of the controls and attributed to maternal body weight decreases. No dose-related or statistical differences were observed between the treated and control groups for number of fetuses/litter or mean gravid uterine weights.

No treatment-related external or visceral fetal malformations/variations were noted. In the mid- and high-dose groups, reduced ossification of the fore- and hind-limbs was indicated by slightly (n.s.) greater ossification scores as compared with the controls. Mean scores for the control, low-, mid-, and high-dose groups were 1.92, 1.99, 2.00, and 2.25, respectively, for the forelimb and 1.65, 1.56, 1.89, and 1.90, respectively, for the hindlimb.

Therefore, the developmental toxicity LOAEL is 1200 mg/kg/day based on increased post-

implantation loss, greater numbers of early and late resorptions and an equivocal decrease in ossification of the fore- and hind-limbs. The developmental toxicity NOAEL is 600 mg/kg/day.

This study is classified as **Acceptable/Guideline** and does satisfy the guidelines for a developmental toxicity study [OPPTS 870.3700 (83-3b)] in rabbits. It should be noted that this study was conducted prior to implementation of the current guidelines. Because the mid- and high-doses exceeded the limit dose of 1000 mg/kg/day, the study is considered sufficient for determining the developmental toxicity potential of permethrin in the rabbit even though a maternal toxicity NOAEL was not identified.

4.4 Reproductive Toxicity

Adequacy of data base for Reproductive Toxicity: The data base for reproductive toxicity is considered complete. No additional studies are required at this time. There is no reproductive toxicity observed.

870.3800 Reproduction and Fertility Effects - Rat

In a three generation reproduction study (MRID 92142092, 120271, 92142037), permethrin, PP557, (purity, 94.0-98.8%; cis:trans 40:60) was administered to groups of 12 male and 24 female Wistar rats in the diet at concentrations of 0, 500, 1000, or 2500 ppm (0, 25, 50, and 125 mg/kg/day, respectively, using a standard conversion factor of 0.05). Two litters were produced by each generation. F_0, F_1, and F_2 parental animals received test or control diet for 12 weeks post weaning and were then paired for mating to produce the A litters. After various rest periods, the F_0, F_1, and F_2 parental animals were remated to produce the B litters. Test diets were administered during mating, gestation and lactation for three successive generations throughout the study. The F_2 parents were mated for a third time, using the same breeding pairs as for the B litters, producing the C litters for a developmental toxicity evaluation. Ten males of the F_1 generation were maintained on experimental diets until they were 54-55 weeks old and were submitted for microscopic examination of selected neurological tissues.

No animals of the parental generations died during the study, although a few were killed because of conditions not related to administration of PP557. There were no dose- or treatment-related effects on body weights, body weight gains, food consumption, or food efficiency.

Treatment-related clinical signs in high-dose parental animals were limited to whole body tremors, occurring in all parental generations (exception: tremors were not observed in the F_0 males) during the first few days of the premating period. In the 2500-ppm groups, the incidence rates for the tremors were 20/24 (F_0 females), 11/12 and 24/24 (F_1 males and females, respectively), and 12/12 and 24/24 (F_2 males and females, respectively). Tremors were also observed in pregnant and lactating females exposed to 2500 ppm PP557. There were no tremors at 0 ppm in any generation. The tremors were intermittent and transient. Neuropathy was not

observed in a special microscopic examination of selected neurological tissues from F_1 males continued on test for one year.

Gross examination at necropsy did not reveal any dose- or treatment-related findings, nor did microscopic examination of grossly abnormal tissues from all parents surviving to scheduled termination and of reproductive tissues from animals suspected of infertility.

Therefore, the LOAEL for systemic toxicity is 2500 ppm (125 mg/kg/day) based on tremors observed in the F_0 females, and the F_1 and F_2 males and females. The systemic toxicity NOAEL is 1000 ppm (50 mg/kg/day).

Mating performance, fertility, and pup growth and survival were not affected by PP557 treatment in the F_1, F_2, and F_3 generations.

In the F_3C litters, there were no developmental effects associated with the administration of PP557 over three generations. The percentages of male fetuses of the 1000- and 2500-ppm groups (39.0 and 44.7%, respectively) were lower than the control value (53.2%), but the effect was not associated with increased resorptions and was not dose-related. Also, no consistent effect on sex ratios was observed in other litters or generations of the study and the effect is not considered to be treatment-related.

Therefore, the reproductive toxicity NOAEL is >2500 ppm (125 mg/kg/day) and the reproductive toxicity LOAEL is not established.

Microscopic examination of F_3B weanlings revealed dose-related increases in centrilobular hypertrophy of the liver. The incidences of slight and moderate centrilobular hypertrophy were dose-related, ranging from 0 to 80% for the males and from 10 to 100% for the females. The HIARC determined that the hypertrophy of the liver is an adaptive and reversible effect and is not considered as an adverse effect. This conclusion is supported by a 90-day rat feeding study (MRID 00054737) where the hepatocellular hypertrophy was observed at 185 mg/kg/day with a NOAEL of 92.9 mg/kg/day. In addition, similar findings might have been observed if histopathological examinations were conducted during the parental evaluation.

The NOAEL for offspring toxicity is >2500 ppm (125 mg/kg/day). The offspring LOAEL is not established.

The study is classified as **acceptable/guideline** and satisfies the requirements for a reproduction study (OPPTS 870.3800 [§83-4a]) in rats.

4.5 Chronic Toxicity

Adequacy of data base for chronic toxicity: The data base for chronic toxicity is considered complete. No additional studies are required at this time.

870.4100a (870.4300) Chronic Toxicity – Rat

In a chronic oral toxicity/oncogenicity study (MRID 92142123), Permethrin was administered to 60 rats/sex/group in the feed at doses of 0, 500, 1000, or 2500 ppm. The mean estimated compound intake for males was 0, 19.4, 36.9, or 91.5 mg/kg/day, respectively, and for females was 0, 19.1, 40.2, or 104 mg/kg/day. Of these animals, 12/sex/group were sacrificed at 52 weeks and the surviving rats were sacrificed at 104 weeks' exposure.

No treatment-related effect on mortality was observed during the the study. No treatment-related effects were seen on tumor induction. During the first two weeks of the study, treatment-related tremors and hypersensitivity were observed in both the high-dose male and female groups. No other treatment-related clinical effects were observed. There were no toxicologically significant effects on body weight, body weight gain, food consumption, or food efficiency. There were no treatment-related effects on ophthalmologic endpoints, hematologic endpoints, clinical chemistry or urinalysis parameters.

Liver changes suggestive of adaptive hypertrophy included increased aminopyrine-N-demethylase activity in all male treatment groups, in the mid- and high-dose female at 52 weeks, and in the high-dose male and female groups at 104 weeks. This was coupled with modestly increased absolute and relative liver weights in the high-dose males and high and low-dose females at 52 weeks and in all male treatment groups and mid-dose females at 104 weeks. Further evidence for adaptive changes included hypertrophy of centrilobular hepatocytes with increased cytoplasmic eosinophilia in the mid- and high-dose male and females at 104 weeks' exposure and increased smooth endoplasmic reticulum proliferation in all treatment groups except low-dose males at 52 weeks and high-dose groups at 104 weeks. Liver changes also included fatty vacuoles that were confirmed by electron microscopy in the mid- and high-dose males at both 52 and 104 weeks and in the high-dose females at 104 weeks. The HIARC evaluated the toxicology database of permethrin and determined that the increased liver weight and hypertrophy observed in the liver are adaptive and reversible effects and are not considered adverse effects.

Under the conditions of this study, the LOAEL is 2500 ppm (91.5 and 104 mg/kg/day for males and females, respectively) based on tremors and hypersensitivity. The NOAEL is 1000 ppm (36.9 and 40.2 mg/kg/day for males and females, respectively).

At the doses tested, Permethrin did not affect the incidence of tumor-bearing animals or the incidence of any specific tumor type in either sex. Permethrin was not carcinogenic to the rat. Dosing was considered adequate based on liver effects and on tremors and hypersensitivity in male and female rats.

This chronic toxicity/oncogenicity study in the rat is **Acceptable/Guideline** and satisfies the guideline requirements for a chronic toxicity/oncogenicity oral study [OPPTS 870.4300 (§83-5a)] in the rat.

870.4100b Chronic Toxicity - Dog

In a chronic oral toxicity study (MRID 00129600), permethrin (92.5%, a.i., cis/trans 32.3/60.2) was administered to beagle dogs (6/sex/group) in corn oil by gelatin capsule at dose levels of 0, 5, 100, or 1000 mg/kg/day for one year. The high dose was lowered from 2000 mg/kg/day after 2 days due to overt toxic reaction to the test material.

There were no mortalities. Neurological clinical signs (tremors, uncoordinated gait, nervousness and convulsions, also excessive salivation and vomiting) were observed in the high-dose group. At the high-dose, decreased body weight gain (37% for males and 33% for females less than control, respectively), decreased food consumption (increased food left uneaten), increased liver weight (+30% and +36% for males and females, respectively) and alkaline phosphatase level (+377% and +220% for males and females, respectively) were reported. At mid-dose, increased liver weight (+25% both sexes) and alkaline phosphatase levels (+134% for males and +99% for females) were observed. Microscopic evaluation of the adrenals showed focal degeneration and necrosis in the cortex with variable inflammatory cell infiltration along with swelling and vacuolization of the cells in the inner cortex at high-dose males and females and at mid-dose males. The liver also showed hepatic cellular swelling at mid- and high-dose males and females.

On April 18, 2002, the HIARC evaluated the toxicology database of permethrin and determined that the observations of increased liver weight, alkaline phosphatase levels, and hepatic cellular swelling are adaptive and reversible effects and are not considered adverse effects (HED Doc# 0050731). **Therefore, the systemic toxicity LOAEL is 1000 mg/kg/day based on clinical neurotoxic signs and decreased body weight gain and food consumption. The NOAEL is 100 mg/kg/day.**

This one-year dog study is classified **Acceptable/Guideline** and satisfies the guideline requirement for a chronic toxicity study in dogs.

4.6 Carcinogenicity

Adequacy of data base for Carcinogenicity: The data base for carcinogenicity is considered complete. No additional studies are required at this time.

870.4200a Carcinogenicity Study - Rat

See previous section 870.4100a.

870.4200b Carcinogenicity (Feeding) - Mouse

In a carcinogenicity study (MRID 00062806, 92142033) FMC 33297 (permethrin, % a.i. not specified, Lot #s MR176 and MR807) was administered to Charles River CD-1 mice (75/sex/dose) in the diet at dose levels of 0, 20, 500, or 2000 ppm for males (equivalent to 0, 3,

71, or 286 mg/kg/day, respectively) and 0, 20, 2500, or 5000 ppm for females (equivalent to 0, 3, 357, or 714 mg/kg/day, respectively) for 24 months.

Mortality was significantly increased in high-dose males after 75 weeks of treatment, but was not significantly different from the control group after 104 weeks. Clinical signs consisting of distended abdomens, ano-genital staining, and alopecia were increased in treated males compared to the control during the first year of treatment, but were not dose-related at 24 months. Insufficient data were provided on body weights (with the exception of final body weights for females), body weight gains, organ weights (with the exception of brain weights of females at study termination), hematology parameters, and gross and microscopic changes for the reviewer to evaluate. An 8% increase in final female body weight was not considered a biologically significant effect. Although difficult to evaluate in the absence of summary data, the effects listed by the study author - transient increased body weights, decreased leucocyte counts and liver and kidney inflammatory changes - do not appear to be toxicologically significant.

A NOAEL and LOAEL for FMC 33297 (permethrin) in mice could not be determined in this study due to major study deficiencies including failure to include summaries of numbers of animals with clinical signs and data on body weights, body weight gains, organ weights, hematology parameters, and gross and microscopic necropsy findings.

A joint FDA-EPA audit of this study conducted in late 1980 at Bio/Dynamics and FMC facilities did not reveal any inadequacies in the conduct or reporting of this study serious enough to compromise the usefulness of these study results for oncogenic evaluation. However, the audit concluded that this study was not useful for assessment of chronic toxicity (HED Doc. #004204).

On December 12, 1988 the HED Cancer Peer Review Committee reviewed the study and concluded that there were statistically significant increases in liver adenoma at all doses for males and at mid- and high-doses for females with a significant dose-related trend in both sexes. Combined liver adenoma/carcinoma also showed statistically significant increases at mid- and high-doses for male and female mice. Statistically significant increases in lung adenomas and combined adenoma/carcinoma at all doses were observed in females only. Carcinoma were increased at all doses but only at HDT that the increase was statistically significant. The incidences of adenoma and carcinoma at mid- and high-doses were outside historical control ranges. There were also significant dose-related trends for lung adenomas, carcinomas and combined adenoma/carcinomas in females. The incidences of lung tumors in male mice (adenoma or carcinoma, or combined) were not statistically significant at any dose, nor was there a dose-related trend for any of them.

This carcinogenicity study in mice is classified as **Acceptable/Guideline (OPPT 870.4200b; §832b)** for evaluation of carcinogenicity. However, this study may not be used for regulatory purpose on assessment of chronic toxicity.

In a carcinogenicity study (MRID 00102110, 92142032) PP557 (94.0-98.9 % a.i., batch/lot #'s P24, P34, P35, P36, P44, P52, BX4, and BX6; cis:trans 40:60) was administered to pathogen free

Alderley Park mice (70/sex/dose) in the diet at dose levels of 0, 250, 1000, or 2500 ppm (equivalent to 0, 26.9, 110.5, or 287.2 mg/kg/day for males and 0, 29.8, 124.2, or 316.1 mg/kg bw/day for females) for up to 98 weeks. Ten males and females per group were set aside for each of 26- and 52-week interim studies during which necropsies were done and hematology, and clinical chemistry parameters were measured.

No significant compound-related effects on mortality or clinical signs were noted. Transient decreases occurred in body weight gain in high-dose males and high-dose females, but at study termination (98 weeks), the final body weight and body weight gain for male mice in the high-dose group were reduced by only 5 and 12%, respectively and the final body weight and body weight gain in females in the high-dose group were unaffected. Food consumption was decreased in the high-dose groups relative to controls during the first week of the study, but was increased at most time points thereafter. No treatment-related changes were seen in hematology or clinical chemistry parameters. Increases of 31 to 48% were seen in liver weights and liver weights corrected for body weight in high-dose males and females compared to the controls. Centrilobular hepatocellular eosinophilia was increased in high-dose males and high-dose females at 52 and 98 weeks compared to the controls. Other liver effects included smooth endoplasmic reticulum proliferation, increased nuclear microbodies, and increased aminopyrine-N-demethylase activity in high-dose animals of both sexes compared to the respective controls. Kidney weights were decreased by 21% in high-dose males, but were slightly increased in high-dose females. Proximal tubular epithelium vacuolation was decreased in number and incidence in high-dose males. The HED HIARC evaluated the toxicology database of permethrin and determined that the increased liver weight and other effects observed in the liver are adaptive and reversible effects and are not considered adverse effects.

Under the conditions of this study, the NOAEL for Permethrin is 2500ppm (287.2 mg/kg/day for males and 316.1 mg/kg/day for females). The LOAEL is not established.

At the doses tested, there was no evidence compared to controls of a significant increase in unusual tumor types or in tumor bearing animals. A non-significant increase in lung adenomas in male mice and in lung adenomas plus carcinomas in female mice at the highest dose (2500 ppm in the diet) was not considered evidence of a carcinogenic effect in light of the high incidences in the control groups of both sexes. In addition to the lungs, major organs examined included liver, kidney, testes, ovary, bladder, brain, and thyroid. The dosing based on toxic response was marginal in both males and females. However, the dosing is considered adequate because higher doses would have resulted in a significant weight deficit in male mice.

This carcinogenicity study in mice is classified **Acceptable/Guideline** and satisfies the guideline requirement for a carcinogenicity study [OPPTS 870.4200b; OECD 451] in mice.

Non-Guideline Carcinogenicity (Feeding) Study - Mouse

In a nonguideline mouse carcinogenicity study (MRID 45597105), Permethrin technical (lot no. PL95-329, 94.7% a.i.) was administered to groups of 50 to 109 Crl:CD-1®(ICR)BR female mice in the diet at 0 or 5000 ppm (equivalent to 780 - 807 mg/kg bw/day) for 39, 52, 65, or 78 weeks.

Groups of mice from all treatment groups were examined immediately after treatment and at weeks 79 and 101. Matching groups of untreated control mice were examined at each interval.

There were no compound-related effects on mortality or body weight. Body weight gain was slightly less in mice treated for 65 or 78 weeks and allowed to recover to week 101 (both 86% of the control weight). The overall food consumption was slightly decreased by 2-3% in some treated groups. The overall food efficiency in the pooled 52-week treatment groups was about 5% less than that of the controls.

At the end of each treatment period, the absolute liver weights were increased by about 44-53% compared to the control groups regardless of the treatment duration. Liver centrilobular hypertrophy and karyomegaly occurred in 87-100% and Kupffer cell hypertrophy was seen in 43-61% of treated animals compared to the controls (0-5%). Centrilobular hypertrophy and Kupffer cell hypertrophy at all dose durations was reversed to or near control levels during the recovery periods. Karyomegaly incidences were reduced by about 11-70% according to the length of the respective recovery periods, but were still present in 25-75% of the treated animals at the 101-week recovery. Inflammatory liver changes were seen in 75-95% of treated animals compared to 37-63% in the controls. The inflammatory liver changes increased in the control mice as a function of age; therefore, recovery was only seen in the treated groups allowed to recover to week 79. Amyloid deposits were increased in treated animals immediately after treatment, and continued to increase during the recovery period. Incidences of eosinophilic foci were significantly increased in the livers of treated groups only after the recovery periods and appeared to be related to the length of the treatment period. The activities of cytochrome P450 (CYP) mixed function oxidases in the livers of animals treated for 52 weeks were expressed both as specific activity (nmol/mg microsomal protein) and the total enzyme activity per liver. Specific activities of total CYP, CYP1A, CYP2B, CYP2E1, and CYP3A were unaffected by treatment, whereas, the specific activity of CYP4A was increased 3-fold. The total enzyme activities per liver of total CYP, CYP1A, CYP2B, CYP2E1, and CYP3A2 were increased in treated animals by 142-283%, and the activity of CYP4A was increased by 829% compared to the control values.

The incidences of Clara cell hyperplasia were increased in the lungs of all treated animals, and the incidences were significantly decreased during the recovery periods to weeks 79 and 101. The specific activities of CYP2B, CYP2E1, and CYP4A in animals sacrificed after 52 weeks of treatment were unaffected by treatment. The total enzyme activities of CYP2E1 and CYP4A expressed as activity/g lung were increased to only 133% and 125%, respectively, of controls.

Significant increases were seen in the incidences of basophilic and eosinophilic hepatocellular adenomas in female mice administered 5000 ppm in the diet for 39, 52, or 78 weeks followed by recovery to week 101 (7% to 10% compared to 1% in controls). The increased incidences were not treatment-duration (dose) related; treatment for 65 weeks resulted in no basophilic adenomas. Eosinophilic adenomas were increased after 78 weeks of treatment and after the recovery period (both 10% compared to 1-2% in controls). The incidences did not increase during the recovery period. No increases in hepatocellular carcinoma incidences were seen and the time to tumor onset for the adenomas was not different in treated animals compared to the controls. Lung

bronchioloalveolar adenoma incidences increased immediately after treatment and continued to increase during the recovery periods compared to the controls. The incidences were 14%, 43%, 47%, 49%, and 49% for the control and 39, 52, 65, and 78 weeks exposure followed by recovery to week 101 ($p<0.01$). The lung adenomas did not occur any earlier in the treated animals than in the control groups, and there was no increase in lung carcinomas in treated animals.

This mouse carcinogenicity study is designed to test the progression and possible reversal of toxic effects including benign liver and lung tumors and is classified as **Acceptable/Non-guideline.**

4.7 Mutagenicity

Adequacy of data base for Mutagenicity: The database for mutagenicity is considered adequate based on pre- 1991 mutagenicity guidelines. The acceptable genetic toxicology studies on permethrin indicate that the compound is not mutagenic in the *Salmonella typhimurium*/ mammalian activation gene mutation and the mouse lymphoma assays. Permethrin is also negative for clastogenicity in a mouse bone marrow micronucleus assay and does not cause unscheduled DNA synthesis in primary rat hepatocytes. There is no evidence of increased dominant lethal mutations in the germinal cells of male mice. Although the submitted mutagenicity studies do not indicate mutagenic activity, two published studies from Barrueco *et al.* (1992, 1994) suggested that permethrin has clastogenic activity (e.g., micronuclei and aberrations inductions) in cultured human lymphocytes and Chinese hamster ovary cells, but only in the absence of S9 activation and at cytotoxic doses.

Gene Mutation

Guideline 870.5100, *Salmonella typhimurium*/ mammalian activation gene mutation MRID 41031107 classification: acceptable	There were no evidence of increased revertant colonies above control in 5 Salmonella strains up to 5000 µg/plate (solubility limit).

Cytogenetics

Guideline 870.5395, Mouse bone marrow micronucleus assay MRID 42723302 classification Acceptable	There was no evidence that permethrin is clastogenic in the bone marrow cells of mice.

Other Genotoxicity

Guideline 870.5550,Unscheduled DNA synthesis (UDS) in primary male rat hepatocytes assay MRID 40943604 classification acceptable	There was no evidence of unscheduled DNA synthesis above control up to 10^{-4} M and possibly 10^{-2} M Limits of cytotoxicity).

4.8 Neurotoxicity

Adequacy of data base for Neurotoxicity: The database for neurotoxicity is considered adequate. There is a concern for neurotoxicity from exposure to permethrin.

870.6100 Delayed Neurotoxicity Study - Hen

(1) In a delayed neurotoxicity study (MRID 00097426), a group of 10 domestic hens were administered 0, 2000, or 4000 mg/kg of permethrin (Lot No.: ZJ; isomer ratio 25 cis:75 trans) in corn oil by oral gavage. An additional group of 10 birds was given 500 mg TOCP/kg as the positive control. All birds were given a single oral dose on study day 0 and observed for 21 days. Birds in the permethrin and negative control groups were redosed on study day 21 and observed for an additional 21 days. Toxicity assessments were limited to clinical observations, assessment of ataxia, body weight measurements, and microscopic evaluation of the spinal cord and sciatic nerve. Acetylcholinesterase and neurotoxic esterase activities were not measured.

No treatment-related clinical signs of toxicity and no effects on body weights or food consumption were observed in birds administered permethrin. Ataxia was not seen in birds treated with the test article and no treatment-related lesions were observed on microscopic examination of the nervous tissues.

Following treatment with TOCP, clinical signs and neurohistopathological lesions indicative of delayed neuropathy were observed in these birds.

Therefore, under the conditions of this study, oral administration of permethrin up to 4000 mg/kg does not produce delayed neuropathy in the hen.

This study is classified **acceptable/guideline** and does satisfy the requirements for a delayed neurotoxicity study [OPPTS 870.6100 (81-7)] in hens. Although a deficiency was that AChE and NTE activities were not measured, the study is considered sufficient for determining the potential of permethrin to produce delayed neurotoxicity in the hen. This study was conducted prior to initiation of current guidelines.

(2) In a delayed neurotoxicity study (MRID 00112933), a group of 15 domestic hens were administered 15 ml of permethrin (Lot No.: not given; isomer ratio 36 cis:58.9 trans, 94.9% a.i.) by oral gavage. Based on a specific gravity of 1.2, mean body weight on study day 0, and not correcting for purity of the test article, the dose to the hens was approximately 9000 mg/kg.

Additional groups were given water as the negative control (n = 10) or 500 mg TOCP/kg as the positive control. All birds were given a single oral dose on study day 0 and observed for 21 days. Birds in the permethrin and negative control groups were redosed on study day 21 and observed for an additional 21 days. Prior to redose, birds in the permethrin group were protected with 10 mg atropine/kg and 50 mg 2-PAM/kg given by intramuscular injection.

Toxicity assessments were limited to clinical observations, assessment of ataxia, measurements of body weights and food consumption, and microscopic evaluation of the brain, spinal cord, and sciatic nerve. Acetylcholinesterase and neurotoxic esterase activities were not measured.

No treatment-related clinical signs of toxicity and no effects on body weights or food consumption were observed in birds administered permethrin. Ataxia was not seen in birds treated with the test article and no treatment-related lesions were observed on microscopic examination of the nervous tissues.

Following treatment with TOCP, clinical signs and neurohistopathological lesions indicative of delayed neuropathy were observed in these birds.

Therefore, under the conditions of this study, oral administration of permethrin does not produce delayed neuropathy in the hen.

This study is classified **acceptable/guideline** and does satisfy the requirements for a delayed neurotoxicity study [OPPTS 870.6100 (§81-7)] in hens. Although a major deficiency was that AChE and NTE activities were not measured, the study is considered sufficient for determining the potential of permethrin to produce delayed neurotoxicity in the hen. This study was conducted prior to implementation of current guidelines.

870.6200 Acute Neurotoxicity Screening Battery

(1) In an acute neurotoxicity study (MRID 43046301), permethrin (95.3% a.i., Lot # PL90-269, cis:trans 50:50) was administered by gavage to Sprague-Dawley rats (4/sex/group) at dose levels of 0, 10, 150, or 300 mg/kg in corn oil. Following administration, the rats were assessed for clinical signs daily. FOB and motor activity assessments were made pre-test and at day 0, (at estimated time of peak effect) and days 7 and 14. After day 14, the rats were sacrificed and the nervous system assessed histopathologically.

Reactions to treatment were noted in the 300 mg/kg treated males and females only. The reactions attributed to treatment included one death (a female), tremors (all animals), staggered gait and gait impairment (8/sex), splayed hindlimbs (2 males, 6 females), decreased forelimb grip strength (21% decrease in males, 13.5% decrease in females) as well as other symptoms occurring in 2 or less animals but not in the controls (convulsion, ataxia, exaggerated hindlimb flexion, increased auditory response, uncoordinated landing). No evidence of compound related neurohistopathology was noted in tissues from animals perfused in vivo. **The LOAEL was 300 mg/kg based on tremors and gait impairment. The NOAEL was 150 mg/kg.**

This acute neurotoxicity study was classified **unacceptable/guideline** because the study was determined to have used inappropriate dose levels and dosing volume of corn oil. A pilot study was reported to indicate clinical signs due to treatment with 50 mg/kg of permethrin when administered as a 10% corn oil solution. The main study was assessed using a 1% corn oil solution and the LOAEL was determined to be 300 mg/kg or 4 times greater. The 1% corn oil solution required dosing the rats with 30 ml/kg for the control and high dose groups and 15 ml/kg for the mid-dose group and 1 ml/kg for the low-dose group. It is considered that dosing with volumes greater than 10 ml/kg results in confounding the interpretation of the study data because of potential effects on compound absorption.

However, the Toxicology Branch has determined that the requirement for an acute neurotoxicity screen study has been satisfied when taken together with another acute oral neurotoxicity study (MRID 45657401, McDaniel and Moser, Neurotoxicology and Teratology 15:71-83, 1993).

(2) In a published literature study (MRID 45657401), permethrin (95%, a.i., cis:trans 50:50) was administered by gavage to Long-Evans rats (8/sex/group) at dose levels of 0, 25, 75, or 150 mg/kg in corn oil. FOB and motor activity were assessed prior to dosing and at 2, 4, 24 and 48 hours after dosing.

At 75 mg/kg, the rats displayed a general pattern of increased excitability and aggressive behavior. Some of the more pronounced responses included abnormal motor movement (3/8, both sexes) decreased grip strength for forelimb (males) and hindlimb (males and females), motor activity (males), and increased body temperature (males). At 150 mg/kg, arousal score (males), righting reflex (males) and approach response score (females) were affected and 7/8 of both sexes had abnormal motor movement and motor activity was further decreased and body temperature was increased >2°C. Slight decreases in body weight (3-4%) were evident. Recovery from the symptoms was within 24 hours. **The LOAEL is 75 mg/kg based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature. The NOAEL is 25 mg/kg.**

The study is classified as **acceptable/nonguideline.** Study is in the form of a literature reprint and was not designed to meet a specific guideline protocol.

870.6200 Subchronic Neurotoxicity Screening Battery

(1) In a subchronic neurotoxicity study (MRID 42933701), permethrin (95.3% a.i., Lot# PL90-269, cis:trans 50:50) was administered via diet to Sprague-Dawley rats (10/sex/group) at dose levels of 0, 250, 1500, or 2500 ppm (0, 15.49, 91.51, or 150.35 mg/kg/day for males and 0, 18.66, 111.37, or 189.63 mg/kg/day for females, respectively) for 13 weeks. Assessments for clinical signs were made daily and FOB and motor activity assessments were made at pretest, and 4, 8, and 13 weeks of the study. Following sacrifice, the control and high dose group rats were perfused and subjected to histopathological assessment.

Reactions to treatment noted in the 1500 ppm dose group included tremors (in 3 males and 5

females), staggered and/or impaired gait, splayed hindlimbs, increased landing feet splay and abnormal posture and decreased grip strength. Only splayed hindlimb and staggered gait were noted in the FOB battery at 1500 ppm. At 2500 ppm, all of the rats had tremors, staggered gait and splayed hindlimbs. Staggered gait and splayed hindlimbs started later. No effects on motor activity or neurohistopathological lesions were noted. Body weight in the high dose group males was 5% decreased and a corresponding slight decrease in food consumption was also noted for this group. **The LOAEL for neurotoxicity is 1500 ppm (91.51 mg/kg/day in males) based on clinical signs (tremors and staggered gait). The NOAEL is 250 ppm (15.49 mg/kg/day).**

This subchronic neurotoxicity study is classified **acceptable/guideline** and satisfied guideline requirement for a subchronic neurotoxicity study.

(2) In a preliminary subchronic oral neurotoxicity study (MRID 00071952), groups of 10 male Wistar rats were administered 2500, 3000, 3750, 4500, 5000, or 7500 ppm of permethrin (PP 557) in the diet for 14 days. The isomeric ratio of the test article (Batch No. P48; 90.4% a.i.) was 39.9% cis and 60.1% trans. Based on a food factor of 0.05 for the rat, doses for the treated groups were 125, 150, 187.5, 225, 250, and 375 mg/kg, respectively. Each treated group had a paired control group consisting of litter mates with similar body weights. Toxicity assessments were limited to clinical observations, measurements of body weights and food consumption, and light and electron microscopic evaluation of the sciatic nerve.

At 7500 ppm six rats were found dead on day 1 and the remainder were sacrificed *in extremis* on day 1 or 2. Prior to sacrifice the animals were observed with convulsive tremors and excessive salivation and those animals for which data were available showed marked weight loss and decreased food consumption. In the 5000-ppm group, two rats were found dead on day 1 and six were sacrificed on day 2; convulsive tremors were observed in one animal prior to death.

Slight to moderate whole body tremors were observed initially in all animals in the 2500 and 3000 ppm groups but almost complete remission occurred by day 5. Moderate tremors were seen in most animals of the 3750 and 4500 ppm groups which lessened during the study but were still evident on day 14. Also at 3750 and 4500 ppm hyperactivity and hypersensitivity to noise were observed mainly during the first 7 days. In the two surviving 5000-ppm animals, slight to moderate tremors were observed until day 10.

Mean absolute body weights of the 3000-, 3750-, and 4500-ppm groups were significantly ($p \leq 0.05$ or 0.01) less than their paired control group weights beginning on day 1 and continuing until termination. Body weights of the surviving 5000-ppm animals were also clearly less than the control. Body weight gains by the 2500-, 3000-, 3750-, 4500-, and 5000-ppm groups were 81%, 60%, 61%, 28%, and 22%, respectively, of their control group level during the first week. However, during the second week body weight gains by all treated groups were 98-104% of the control levels with the exception of the 5000-ppm group which was 83% of the controls.

Food consumption for the first week was significantly ($p \leq 0.01$) reduced in all treated groups to 67-84% of their paired control group levels. Consequently, food utilization was increased in a

dose-related manner for all treated groups as compared with the control groups.

The number of rats with degenerating nerve fragments in the treated and paired control groups was 5/10 each at 2500 ppm, 8/10 and 2/9, respectively, at 4500 ppm, and 6/10 and 2/10, respectively, at 5000 ppm. The number of fragments per nerve ranged from 1-5 for animals in the control, 2500-, and 4500-ppm groups and for animals in the 5000 ppm group that died or were killed intercurrently. In contrast, the two surviving rats in the 5000 ppm group had 19 and 44 fragments respectively.

Nerves from rats in the 2500- and 5000-ppm groups were also examined by electron microscopy. No treatment-related abnormalities were observed in the 2500-ppm group. At 5000 ppm, the ultrastructural changes observed were similar in animals that died and in the two rats that survived to scheduled termination. In the unmyelinated nerves, 7/7 rats given 5000 ppm had degenerative changes including axonal swelling, disorganization of the neurofilaments, an increase in multivesicular-type and vesicular structures, and vacuolation. Only a minimal increase in vesicular structures was observed in 3/7 paired controls. Mild to marked vacuolation of the Schwann cell cytoplasm was seen in 5/7 rats treated with 5000 ppm and mild vacuolation was seen in 2/7 controls. Also in the Schwann cells, dense bodies occurred in the cytoplasm of 6/7 treated rats vs. 0/7 controls and hypertrophy and increased nuclear chromatin with multiple nucleoli were seen in 5/7 treated and 1/7 control rats. Intercellular vacuolation was observed in 4/7 treated and 1/7 control rats.

Therefore, the systemic and neurotoxicity LOAEL is 2500 ppm (125 mg/kg) based on clinical signs of toxicity and decreases in body weight gain and food consumption. The systemic and neurotoxicity NOAEL was not identified for this preliminary study.

This study is classified **acceptable/nonguideline** and does not satisfy the requirements for a subchronic oral neurotoxicity study [OPPTS 870.6200 (§82-7)] in rats. The study is sufficient for the purposes for which it was intended, as an evaluation of the effects of feeding high concentrations of PP 557 to male rats on body weights, food consumption, clinical signs, and microscopic lesions in the sciatic nerve.

(3) In a subchronic oral neurotoxicity study (MRID 40766807), Sprague-Dawley rats (10/sex/group) were administered Permethrin (98%, 40:60 cis/trans, Lot No. PL85-216) in acetone at concentrations of 0, 100, 200, or 400 mg/kg/day in the diet for 90 days (main study). Two control groups were included, one was an untreated control group and the other was a vehicle (acetone treated diet) control group. After the 90 days, the rats in the main study were sacrificed by a special procedure designed to allow for fixation of the nervous system *in situ*. The experiment also included a special recovery component that consisted of 10 male and 10 female rats in the 400 mg/kg/day and untreated control groups; these animals were sacrificed 6 weeks after the completion of dosing after being maintained on untreated control diet. Neurological tissues from control and high-dose animals were examined microscopically. Functional observational battery (FOB) and motor activity testing were not performed.

There were no treatment-related deaths. Clinical signs included hyperexcitability, intermittent tremors, and irritability in mid-dose males during the first 3 weeks of treatment and intermittent tremors in mid-dose females during the first week of treatment. High-dose rats exhibited hyperexcitability, intermittent and continuous tremors, twitching, nystagmus (males only) and combativeness (males only) throughout the treatment period. Body weight gain was decreased 6 to 13% in high-dose males from treatment week 11 to post-dosing week 2; and 5 to 9% in high-dose females compared to controls from weeks 3 to 13. No treatment-related food consumption effects were noted. There were no gross lesions associated with treatment and there were no microscopic observations indicative of a neurotoxic effect.

The systemic LOAEL is 200 mg/kg/day based on tremors and irritability. The systemic NOAEL is 100 mg/kg/day. The NOAEL is > 400 mg/kg/day with respect to morphological and histological changes.

This study is classified **acceptable/nonguideline.** The data provide useful information suggesting no morphological or histological effects in rats fed 400 mg/kg/day in the diet for 90 days.

870.6300 Developmental Neurotoxicity Study

No developmental neurotoxicity study is available. Based on the weight of evidence, the HIARC concluded that there is a concern for developmental neurotoxicity resulting from exposure to permethrin. A developmental neurotoxicity study (DNT) is required for permethrin and is considered as a data gap.

4.9 Metabolism

Adequacy of data base for metabolism: All submitted metabolism studies on permethrin were classified unacceptable/guideline based on deficiencies in level of detail provided which prevent verification/validation of findings (e.g., insufficient data regarding characterization of recovered radioactivity, no dose confirmation, no lot/batch numbers for the test article). However, consider all metabolism studies together, it adequately provides information on absorption, distribution, and excretion. No additional studies are required at this time.

870.7485 Metabolism - Rat

(1) In a series of metabolism and disposition experiments (MRID 00089006, 00054719, and MRID 92142041 [summary of MRID 00089006], and MRID 92142042 [summary of MRID 00054719]), male and female Wistar-derived rats were placed on various oral treatment regimens with [^{14}C-alcohol]permethrin ([^{14}C-cyclopropyl]permethrin) or [^{14}C-acid]permethrin ([^{14}C-benzyl]permethrin). For MRID 00054719, [^{14}C-acid]permethrin (>98% purity, 53:47, cis trans ratio; no lot or batch no.) or [^{14}C-alcohol]permethrin (99% purity, 40.5:59.5 cis:trans ratio; no lot or batch no.) were diluted as needed with nonlabeled permethrin (93.6% purity, 40.5:59.5,

cis:trans ratio; no lot or batch no.) and given by gavage to two male and two female rats at a dose of 6.5 mg/kg for quantitative and qualitative assessment of excretion. In MRID 00089006, tissue distribution and blood kinetics were assessed in male and female Wistar-derived rats given repeated or single oral doses of [^{14}C-acid]permethrin (>98% purity; 53:47, cis:trans ratio; no lot or batch no.) or [^{14}C-alcohol]permethrin (99% purity, 38:62 cis:trans ratio; no lot or batch no.)

These studies provided information on the excretion and tissue burdens of permethrin in rats following single or multiple oral doses of either alcohol ([^{14}C-cyclopropyl]permethrin) or acid [^{14}C-benzyl]permethrin). Based upon a limited number of rats, overall recovery was 93.7% to 101% regardless of label position. Following a single oral dose of 6.5 mg/kg, most radioactivity (58-65%) from a single dose of the [^{14}C-alcohol] permethrin was eliminated via the urine over a 7-day period with much of the remainder (29-43%) being excreted in the feces. Urinary excretion of radioactivity following a single dose of [^{14} C-acid] permethrin was slightly less and fecal excretion correspondingly greater. Results of tissue distribution and autoradiographic experiments showed that most radioactivity was associated with adipose tissue and, initially, with the gastrointestinal tract and organs/tissue associated with excretory function. Following oral administration to rats, most permethrin-associated radioactivity appears to be excreted within 48 hours. Following multiple doses, radioactivity in adipose tissue appears to be greater for [^{14}C-alcohol] permethrin than for [^{14}C-acid] permethrin. This is also consistent with blood kinetics data showing lower radioactivity (C_{max}) in the blood of rats receiving [^{14}C-acid] permethrin. Upon cessation of dosing, radioactivity levels in adipose tissues declined. There was no attempt to identify the metabolites in these studies.

This metabolism study in the rat is classified **Unacceptable/Guideline** and does not satisfy the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in rats. The unacceptability is the result of deficiencies in level of detail provided which prevent verification/validation of findings (e.g., unreadable data, environmental conditions not reported, no dose confirmation, no lot/batch numbers for the test article).

(2) In a metabolism study (MRID 00102185), male Wistar-derived rats were given a single low dose (2.0 mg/rat) or single high dose (20 mg/rat) of permethrin ([^{14}C-cyclopropane]permethrin, 40:60 cis-trans ratio and non-labeled permethrin, 38.2:59.3 cis-trans ratio; no purity or lot/batch nos. for either) intragastrically. Feces and urine collected one day prior to dosing and for three days postdose were analyzed for radioactivity and metabolites.

These experiments provided an initial and cursory effort at identification and quantitation of major metabolites in the urine and feces of rats following single oral doses (2 or 20 mg/rat) of [^{14}C-cyclopropane]permethrin. Approximately 78.5% of the administered radioactivity was recovered over the 3-day experimental period (dose group not specified). A conjugated metabolite, 3-(2,2-dichlorovinyl)-1-methylcyclopropane-1,2-dicarboxylic acid, was identified in both the urine and feces that reportedly accounted for approximately 2.2% of the administered dose. No additional data were provided regarding characterization of the remaining recovered radioactivity.

This metabolism study in the rat is classified **Unacceptable/Guideline** and does not satisfy the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in rats. The unacceptability is the result of deficiencies in level of detail provided which prevent verification/ validation of findings (e.g., insufficient data regarding characterization of recovered radioactivity, no dose confirmation, no lot/batch numbers for the test article).

(3) In a metabolism study (MRID 00065903), groups of rats were given oral doses (1.6-4.8 mg/kg) of radiolabeled isomers ([^{14}C-acid] or [^{14}C-alcohol] labeled) of permethrin (radiochemical purity >99%; no lot/batch nos.) in dimethylsulfoxide vehicle. Metabolism and disposition was assessed over a 4 to12-day period

Recovery of administered radioactivity was 97-100% at 12 days after administration of the test article. The test material appeared to be rapidly absorbed and excreted in the urine and feces. Quantitative differences in excretion profile were characterized by greater amounts of *trans*-permethrin in the urine suggesting greater metabolism of the *trans* isomer than the *cis* isomer. Most of the urinary metabolites and some fecal metabolites appeared to be hydroxylation products, and glucuronide and sulfate conjugates of these products. Qualitative differences in metabolite profiles were also noted for the two isomers. Excretion of radioactivity via expired air was negligible. Fat tissue, liver, and kidney contained the highest levels of radioactivity, although there did not appear to be potential for sequestration at the dose regimens studied. The study authors concluded that the metabolism in rats of the *cis* and *trans* isomers of permethrin was characterized by ester cleavage, oxidation at the *cis* or *trans* methyl group of the dimethyl moiety, and oxidation at the 2' or 4' position of the phenoxy group.

This review is conducted on a best available copy of the report. However, most data tables and some text were not legible and, therefore, verification of the study authors' interpretations and conclusions was not possible. This metabolism study in the rat (MRID 00065903), apparently a draft manuscript for submission to the J. of Agricultural and Food Chemistry, is classified **Unacceptable/Guideline** and does not satisfy the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in rats. *Although the study appeared to be an in-depth examination of the metabolism of the *cis* and *trans* isomers of permethrin in the rat and could potentially achieve guideline requirements, the resulting study report was generally unreadable and exhibited notable deficiencies.

870.7485 Metabolism - Dog

Two metabolism studies were conducted using adult Beagle dogs. In MRID 0054721, groups of four male and four female beagle dogs were given [^{14}C-alcohol]permethrin (PP557; no lot/batch nos.; 59.7 mCi/mM; purity not reported) or [^{14}C-acid]permethrin (PP557; no lot/batch nos.; 1.87 mCi/mM; purity 99%) as a single oral dose (6.5 mg/kg and 6.2 mg/kg, respectively) in a gelatin capsule. Excreta were collected over a 7-day period and tissues collected and analyzed at termination. In MRID 00042160, two beagle dogs (gender not specified) were given 10 daily doses (1.0 mg/kg via gelatin capsules) of [^{14}C-alcohol]permethrin (PP557; no lot/batch nos.; 59.7 mCi/mM; purity not reported). Excreta were collected after seven days and adipose tissues

analyzed at termination.

These experiments provided preliminary information regarding the metabolism and disposition of permethrin in dogs. Data were insufficient for determination of definitive mass balance for administered radioactivity. Following oral administration of a single dose of [^{14}C-alcohol]permethrin (6.5 mg/kg) or [^{14}C-acid]permethrin (6.2 mg/kg), approximately 84-87% of administered radioactivity was eliminated via the feces and urine in 24-48 hours (MRID 000054721). Fecal excretion (~45-56% of dose) was somewhat greater than urinary excretion (~30-38% of dose) and the rate of excretion was slightly less for the [^{14}C-alcohol]permethrin. At seven days postdose, radioactivity was detected in the tissues selected for analysis (peri-renal and subcutaneous fat, liver, kidney, lung, heart, blood, and brain). The highest tissue levels (0.5-0.7 µg eq./g) were found in the fat tissues. Although radioactivity was detected in all tissues seven days following the single oral dose, levels were minimal and there was no evidence for significant sequestration. Following a single oral dose, TLC analysis of organic solvent extracts revealed up to four metabolites in the urine and six in the feces, none of which were characterized. The excretory pattern for dogs given multiple doses of [^{14}C-alcohol]permethrin (1.0 mg/kg/day for 10 days) (MRID 00042160) was similar to that observed for the single dose study. The repeat-dose study also provided preliminary data showing a shift in the cis:trans ratio (an increase in the cis isomer) of residues in peri-renal and subcutaneous fat, and noted that this shift was indicative of a preferential metabolism of the trans isomer.

These metabolism/disposition studies in the dog are classified **Unacceptable/Non-Guideline** and do not satisfy the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in dogs. The unacceptability is the result of deficiencies in level of detail provided which prevent verification/validation of findings (e.g., insufficient data regarding characterization of recovered radioactivity, no dose confirmation, no lot/batch numbers for the test article, mass balance data lacking in MRID 00042160). Furthermore, the studies were conducted prior to GLP Guidelines and lacked quality assurance statements.

870.7600 Dermal Absorption - Rat

In a dermal penetration study in rats (MRID 43169001), four groups of 24 male rats (Wistar strain) were dosed dermally at 9.1, 0.86, 0.08, or 0.004 mg ^{14}C-permethrin per rat applied in concentrated 2EC formulation or water diluted formulation. The rats were sacrifced at 0.5, 1, 2, 4, 10, and 24 hours after application to assess for dermal pentration.

Total recovery ranged from 95.86 ± 2.81% for the 9.1 mg group to 99.77 ± 3.53% for the 0.08 mg group indicating good experimental efficiency. Systemically absorbed and the total of the systemically absorbed plus potentially absorbable (content of stratum corneum and residual skin) varied widely because permethrin adhered to the skin. The reviewer noted that there was a general progression of increased permethrin absorption up to 24 hours without an indication of a plateau. Thus, exposure to permethrin for period of longer than 24 hours may result in higher percentage of the exposed dose being absorbed from corneum. The HIARC determined that a dermal absorption factor of 30% is considered to be a conservative estimate for risk assessment

because neurotoxicity signs were not observed in a 21-day dermal toxicity study at doses up to 500 mg/kg/day whereas they were observed in the acute or subchronic neurotoxicity studies at a dose level of 75 or 100 mg/kg/day, respectively.

5.0 TOXICITY ENDPOINT SELECTION

5.1 See Section 9.2 for Endpoint Selection Table.

5.2 Dermal Absorption

Dermal Absorption Factor: 30 %

The dermal absorption factor is required for residential/occupational risk assessment since oral doses were selected for these exposure periods.

5.3 Classification of Carcinogenic Potential

5.3.1 Conclusions of Carcinogenic Potential

The CARC concluded that permethrin showed evidence of carcinogenicity based on the following:

- Permethrin induced reproducible benign lung tumors in female mice and liver tumors in both male and female CD-1 mice. The new carcinogenicity/reversibility study confirms the permethrin-induced benign lung and liver tumors in female mice seen in the FMC Mouse II study. The CARC also reconsidered the 1995 Pathology Work Group (PWG) report on a reassessment of the lung tumor slides from the FMC mouse II study and determined it to be acceptable. The PWG report indicated that permethrin induced benign lung tumors. The CARC also confirmed a previous CPRC report that there were statistically significant increases in liver adenomas in male mice at all doses (and outside historical control range at all doses) with a significant dose-related trend in the FMC Mouse II study (Memo, E. Rinde, April 7, 1989, "Peer Review of Permethrin").

- No statistically significant increase in malignant lung or liver tumors were seen in male or female mice in either of the above mentioned studies.

- There was no evidence of carcinogenicity in male or female Wistar rats. However, the CPRC (1989) questioned the adequacy of the permethrin doses to assess carcinogenic potential in female rats. The CARC revisited the adequacy of dosing issue and determined that the dosing was adequate to assess carcinogenicity in both sexes.

- The evidence of carcinogenicity in the Long-Evans rat study was equivocal. The CPRC (1989) also stated that rats (both sexes) did not receive adequate doses. The CARC concluded that the adequacy of the dose can not be resolved at this time for the Long-

Evans rats.

- The acceptable genetic toxicology studies on permethrin indicate that the compound is not mutagenic in the *Salmonella typhimurium*/mammalian activation gene mutation and the mouse lymphoma assays. Permethrin is also negative for clastogenicity in a mouse bone marrow micronucleus assay and does not cause unscheduled DNA synthesis in primary rat hepatocytes. There is no evidence of increased dominant lethal mutations in the germinal cells of mice. Although the submitted mutagenicity studies do not indicate mutagenic activity, the CARC acknowledged that two published studies from Barrueco *et al.* (1992, 1994) suggested that permethrin has clastogenic activity (e.g., micronuclei and aberrations inductions) in cultured human lymphocytes and Chinese hamster ovary cells, but only in the absence of S9 activation and at cytotoxic levels.

- Structure activity relationship (SAR) indicated that Cypermethrin is a close structural analogue to permethrin. Cypermethrin is classified as a Category "C" carcinogen (possible human carcinogen) based on female mice lung tumors (adenomas and combined) with no Q_1^* (Cancer Peer Review Committee, 1988).

- There are no mode of action studies available at this time.

5.3.2 Classification of Carcinogenic Potential

In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July 1999), the CARC, by majority vote, classified permethrin as **"Likely to be Carcinogenic to Humans"** by the oral route.

5.3.3 Quantification of Carcinogenic Potential

The CARC recommended a low dose linear extrapolation model with a Q_1^* of **9.567×10^{-3}** $(mg/kg/day)^{-1}$ be applied to the animal data for the quantification of human risk, based on female mouse lung adenoma and/or carcinoma combined tumor rates.

6.0 FQPA CONSIDERATIONS

6.1 Special Sensitivity to Infants and Children

The HIARC determined that there is no evidence (qualitative or quantitative) for increased susceptibility following *in utero* and/or pre-/post-natal exposure in the developmental toxicity studies in rats and rabbits and multi-generation reproduction studies in rats. Since there is no developmental or reproductive toxicity observed in the developmental studies in rats and rabbits or reproduction study in rats, the HIARC concluded that there are no concerns or residual uncertainties for pre- and post-natal toxicity.

6.2 Recommendation for a Developmental Neurotoxicity Study

Evidence of neurotoxicity was shown in the acute and subchronic neurotoxicity studies and other subchronic and chronic toxicity studies in dogs and rats. In addition, the subchronic neurotoxicity studies showed increased incidence of microscopic lesions associated with neurotoxic effects at high doses. Based on the weight of evidence presented, the HIARC concluded that there is a concern for developmental neurotoxicity resulting from exposure to permethrin and a developmental neurotoxicity study (DNT) is required for permethrin.

6.3. Recommendation for Special FQPA Safety Factor(s)

The HIARC determined that a **10X DB_{UF}** was required for **acute and chronic dietary risk assessments** as well as for **residential (non-dietary) exposure scenarios.**

7.0 OTHER ISSUES

No other issues were identified at this time.

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9.0APPENDICES
Tables for Use in Risk Assessment

9.1 Toxicity Profile Summary Tables

9.1.1 Acute Toxicity Table

See Section 4.1

9.1.2 Subchronic, Chronic and Other Toxicity Tables

Guideline No./ StudyType/	MRID Nos. Doses/Classification	Results
870.3200 21-Day dermal toxicity (1989)	41143801,42653301 Ph III Summ: 92142030 0, 50, 150, 500 mg/kg/day Acceptable/guideline	The systemic NOAEL was 500 mg/kg/day (the highest dose tested), the systemic LOAEL was not established. The dermal LOAEL was 50 mg/kg/day based on skin irritation. A dermal NOAEL was not identified.
870.3465, 82-4 15-Day inhalation toxicity	00096713 0, 0.0061, 0.042, 0.583 mg/L Acceptable/non-guideline	The LOAEL is 0.583 mg/L in male and female rats based on body tremors and hypersensitivity to noise. The NOAEL is 0.042 mg/L.
870.3700a Prenatal developmental in Rat , (1988)	40943603 0, 15, 50, 150 mg/kg/day Acceptable/Guideline	The maternal toxicity LOAEL is 150 mg/kg/day based on clinical signs of toxicity and decreased body weight gain and food consumption. The maternal toxicity NOAEL is 50 mg/kg/day.the developmental toxicity LOAEL is 150 mg/kg/day based on decrease in fetal body weights and an increase in the incidence rate of short length extra ribs. The developmental toxicity NOAEL is 50 mg/kg/day.
870.3700b Prenatal developmental in Rabbit	92142091,40943602, 92142036 0, 600, 1200, 1800 mg/kg/day Acceptable/guideline	The maternal toxicity LOAEL is estimated to be <600 mg/kg/day based on decreased body weight gain. The maternal toxicity NOAEL is not identified. The developmental toxicity LOAEL is 1200 mg/kg/day based on increased post-implantation loss, greater numbers of early and late resorptions and an equivocal decrease in ossification of the fore- and hind-limbs. The developmental toxicity NOAEL is 600 mg/kg/day.
870.3800 Reproduction and fertility effects	00102108 00120271 92142092 92142037 0, 500,1000,2500 ppm (0, 25,50,125 mg/kg/day) Acceptable/guideline	The LOAEL for systemic toxicity is 2500 ppm (125 mg/kg/day) based on tremors observed in the F_0 females, and the F_1 and F_2 males and females. The systemic toxicity NOAEL is 1000 ppm (50 mg/kg/day). The reproductive toxicity NOAEL is ≥2500 ppm (125 mg/kg/day) and the reproductive toxicity LOAEL is not identified. The NOAEL for offspring growth and development is ≥2500 ppm (125 mg/kg/day) and the offspring LOAEL is not identified.

Guideline No./ StudyType/	MRID Nos. Doses/Classification	Results
870.4300 Chronic toxicity in Rats (1977)	92142123 0, 500, 1000, or 2500 ppm 0, 19.4, 36.9, 91.5 mg/kg/day (M) 0, 19.1, 40.2, 104 mg/kg/day (F) Acceptable/guideline	The chronic toxicity LOAEL is 2500 ppm (91.5 mg/kg/day for males and 104 mg/kg/day for females), based on tremors and hypersensitivity. The NOAEL is 500 ppm (36.9 mg/kg/day for males and 19.4 mg/kg/day for females). No tumor
870.4100b Chronic toxicity in dogs (1982)	00129600 0,5,100,1000 mg/kg/day (capsule) Acceptable/Guideline	The systemic toxicity LOAEL is 1000 mg/kg/day based on clinical neurotoxic signs and decreased body weight gain and food consumption. The NOAEL is 100 mg/kg/day.
870.4200b Carcinogenicity in mice	00062806, 92142033 0, 3, 71, 286 mg/kg/day (M) 0, 3, 357, 714 mg/kg/day (F) Acceptable/guideline	There were statistically significant increases in liver adenoma at all doses for males and at mid- and high-doses for females with a significant dose-related trend in both sexes.
870.4200b Carcinogenicity in mice	00102110, 92142032 0, 26.9, 110.5, 287.2 mg/kg/day (M). 0, 29.8, 124.2, 316.1 mg/kg/day (F) Acceptable/guideline	There was no evidence of significant increase in unusual tumor types. A non-significant increase in lung adenomas in males and in lung adenomas plus carcinomas in females was seen at the highest dose.
870.4200b Carcinogenicity in mice	45597105 0, 5000 ppm (Females only) (0, 780-807 mg/kg/day) Acceptable/non-guideline	There were significant increases in the incidences of lung bronchioloalveolar adenomas in mice. The increased incidences of basophilic hepatocellular adenoma did not show a relationship to the treatment duration. No progression to carcinoma was observed in the lung or liver.
870.5100 Gene mutation Salmonella typhimurium	41031107 Acceptable/guideline	There were no evidence of increased revertant colonies above control in 5 Salmonella strains up to 5000 µg/plate (solubility limit).
870.5550 Unscheduled DNA	40943604 Acceptable/guideline	There was no evidence of unscheduled DNA synthesis above control up to 10^{-4} M and possibly 10^{-2} M Limits of cytotoxicity).
870.5395 Mouse Bone Morrow Micronucleus	42723302 Acceptable/guideline	There was no evidence that permethrin is clastogenic in the bone marrow cells of mice.
870.6200 Acute Neurotoxicity	43046301 45657401 Acceptable when considered together	NOAEL = 25 mg/kg/day LOAEL = 75 mg/kg/day based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature.

Guideline No./ StudyType/	MRID Nos. Doses/Classification	Results
870.6200 Subchronic neurotoxicity	00071952 2500,3000,3750,4500, 5000, 7500 ppm Acceptable/nonguideline	The systemic and neuro- toxicity LOAEL is 2500 ppm (125 mg/kg) based on clinical signs of toxicity and decreases in body weight gain and food consumption. The systemic and neuro- toxicity NOAEL was not identified for this preliminary study.
870.6200b Subchronic neurotoxicity Nonguideline	40766807 0, 100, 200, 400 mg/kg/day Acceptable/nonguideline	The systemic LOAEL is 200 mg/kg/day based on tremors and irritability. The systemic NOAEL is 100 mg/kg/day. The NOAEL is > 400 mg/kg/day with respect to morphological and histological changes.
870.6100b Delayed Neurotox in the Hen	00112933 approx. 9000 mg/kg (94.9% a.i.) cis:trans 36:58.9 Acceptable/guideline	Oral administration of permethrin does not produce delayed neuropathy in the hen.
870.6100b Delayed Neurotox in the Hen	00097426 0, 2000,4000 mg/kg cis:trans 25:75 Acceptable/guideline	Oral administration of permethrin up to 4000 mg/kg does not produce delayed neuropathy in the hen.

9.2 Summary of Toxicological Dose and Endpoints for permethrin for Use in Human Risk Assessment[1]

Summary of Toxicology Endpoint Selection for Permethrin

Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Special FQPA SF* and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (Females 13-50 years of age)	**Acute RfD** = No applicable	An appropriate endpoint attributable to a single dose was not identified.	
Acute Dietary (General population including infants and children	NOAEL = **25** mg/kg/day UF = **1000** **Acute RfD** = 0.025 mg/kg/day	FQPA SF = 1X **aPAD** = acute RfD / FQPA SF = 0.025 mg/kg/day	**Acute Neurotoxicity Study in Rats** LOAEL = **75** mg/kg/day based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature
Chronic Dietary (All populations)	NOAEL= **25** mg/kg/day UF = **1000** **Chronic RfD** = 0.025 mg/kg/day	FQPA SF = 1X **cPAD** = chronic RfD / FQPA SF = 0.025 mg/kg/day	**Acute Neurotoxicity Study in Rats** LOAEL = **75** mg/kg/day based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature
Short-Term Incidental Oral (1 - 30 Days)	NOAEL = 25 mg/kg/day	**Residential** LOC for MOE = 1000	**Acute Neurotoxicity Study in Rats** LOAEL = **75** mg/kg/day based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature
Intermediate-Term Incidental Oral (1 - 6 Months)	NOAEL = 25 mg/kg/day	**Residential** LOC for MOE = 1000	**Acute Neurotoxicity Study in Rats** LOAEL = **75** mg/kg/day based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Short-Term Dermal (1 - 30 days)	Oral study NOAEL= 25 mg/kg/day (dermal absorption rate = 30%)	**Residential** LOC for MOE = 1000 **Occupational** LOC for MOE = 100	**Acute Neurotoxicity Study in Rats** LOAEL = **75** mg/kg/day based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature
Intermediate-Term Dermal (1 - 6 Months)	Oral study NOAEL= 25 mg/kg/day (dermal absorption rate = 30%)	**Residential** LOC for MOE = 1000 **Occupational** LOC for MOE = 100	**Acute Neurotoxicity Study in Rats** LOAEL = **75** mg/kg/day based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature
Long-Term Dermal (> 6 Months)	Oral NOAEL= 25 mg/kg/day (dermal absorption rate = 30%)	**Residential** LOC for MOE = 1000 **Occupational** LOC for MOE = 100	**Acute Neurotoxicity Study in Rats** LOAEL = **75** mg/kg/day based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature
Short-Term Inhalation (1 - 30 days)	Inhalation NOAEL= 0.042 mg/l (Converts to oral equivalent of 11 mg/kg/day)	**Residential** LOC for MOE = 1000 **Occupational** LOC for MOE = 100	**15-Day Inhalation Study in Rats** LOAEL = 0.583 mg/l (converts to oral equivalent of 154 mg/kg/day) based on body tremors and hypersensitivity to noise.
Intermediate-Term Inhalation (1 - 6 Months)	Inhalation NOAEL= 0.042 mg/l (Converts to oral equivalent of 11 mg/kg/day)	**Residential** LOC for MOE = 1000 **Occupational** LOC for MOE = 100	**15-Day Inhalation Study in Rats** LOAEL = 0.583 mg/l (converts to oral equivalent of 154 mg/kg/day) based on body tremors and hypersensitivity to noise.
Long-Term Inhalation (>6 Months)	Inhalation NOAEL= 0.042 mg/l (Converts to oral equivalent of 11 mg/kg/day)	**Residential** LOC for MOE = 1000 **Occupational** LOC for MOE = 100	**15-Day Inhalation Study in Rats** LOAEL = 0.583 mg/l (converts to oral equivalent of 154 mg/kg/day) based on body tremors and hypersensitivity to noise.

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Cancer (Oral, dermal, inhalation)	Classification: "Likely to be Carcinogenic to Humans" with Q_1* $(mg/kg/day)^{-1} = 9.567 \times 10^{-3}$		

NOTE: The Special FQPA Safety Factor recommended by the HIARC **assumes** that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

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Chemical:	**Permethrin**
PC Code:	**109701**
HED File Code	**13000 Tox Reviews**
Memo Date:	**12/16/2003**
File ID:	**TX0050721**
Accession Number:	**412-04-0139**

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